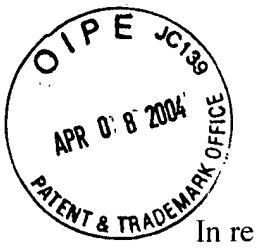
00766.000043 PATENT APPLICATION



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Ram R. Shukla
AKIHIRO UMEZAWA, ET AL.	)	
	:	Group Art Unit: 1632
Application No.: 09/749,728	)	
	:	
Filed: December 28, 2000	)	
	:	
For: THE CELL HAVING THE POTENTIALITY OF DIFFERENTIATION INTO CARDIOMYOCYTES	)	
	:	April 8, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF TRANSLATION OF
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Sir:

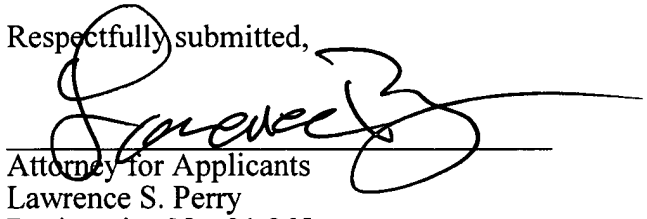
Enclosed to complete the record and for the Examiner's convenience is an English translation of the International Preliminary Examination Report in the above-identified application.

Relevance of the Cell Technology article cited in the February 27, 2004 Information Disclosure Statement is discussed therein (see Document 8, last paragraph).

Entry hereof is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,



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NY_MAIN 419430v1

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1217WO3	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP00/09323	International filing date (*day/month/year*) 27 December 2000 (27.12.00)	Priority date (*day/month/year*) 28 December 1999 (28.12.99)
International Patent Classification (IPC) or national classification and IPC C12N 5/06, 5/08, C12P 21/08, C12Q 1/02, A61K 35/28, 33/44, A61P 9/06, 9/04 // A61K 38/18, C12N 15/12		
Applicant KYOWA HAKKO KOGYO CO., LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

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3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 July 2001 (19.07.01)	18 January 2002 (18.01.2002)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/09323

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/09323

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 76,78

because:

☒ the said international application, or the said claims Nos. 76,78 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet for continuation of Box III . 1.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

The invention set forth in Claim 76 relating to a "method for cardiac regeneration after damage due to heart disease", and the invention set forth in Claim 78 relating to a "process for transporting a wild gene for a genetic variant in a congenital heart condition specifically to the myocardium", essentially pertain to methods for diagnosis or treatment of the human body by therapy, and thus relate to subject matter which does not require international preliminary examination by this International Preliminary Examining Authority, under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP 00/09323

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	8-18,25,48-51,59,66-75,77,79-85,87-89	YES
	Claims	1-7,19-24,26-47,52-58,60-65,86,90-91	NO
Inventive step (IS)	Claims		YES
	Claims	1-75, 77, 79-91	NO
Industrial applicability (IA)	Claims	1-75, 77, 79-91	YES
	Claims		NO

2. Citations and explanations

Document 1: S. Makino et al., "Cardiomyocytes can be generated from marrow stromal cells in vitro", J. Clin. Invest. (March 1999), Vol. 103, No. 5, pp. 697-705

Document 2: Keichi Fukuda, "Kotsuzui saibou kara no shinkin saibou no yuudo", Human Cell (September 1999), Vol. 12 No. 3, pp. 159-162

Document 3: K. Guan et al., "Embryonic stem cell differentiation models: cardiogenesis, neurogenesis, epithelial and vascular smooth muscle cell differentiation in vitro", Cytotechnology (May 1999), Vol. 30, No. 1-3, pp. 211-226

Document 4: E. Kolossov et al., "Functional characteristics of ES cell-derived cardiac precursor cells identified by tissue-specific expression of the green fluorescent protein", J. Cell. Biol. (1998), Vol. 143, no. 7, pp. 2045-2056

Document 5: J. M. Lehmann et al., "An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ)", Proc. Natl. Acad. Sci.

USA (1995), Vol. 270, No. 22, pp. 12953-12956

Document 6: H. E. Young et al., "Human pluripotent and progenitor cells display cell surface cluster differentiation markers CD10, CD13, CD56 and MHC Class I", Proc. Soc. Exp. Biol. Med. (1999), Vol. 221, No. 1, pp. 63-71

Document 7: N. Kröger et al., "Difference between expression of adhesion molecules on $CD34^+$ cells from bone marrow and G-GSF-stimulated peripheral blood", Stem Cells (1998), Vol. 16, No. 1, pp. 19-53

Document 8: "HIV bekutaa wo mochiita seiketsu kansaibou he no iden donyuu", Saibo Kogaku (June 1999), Vol. 18, No. 6, pp. 848-851

Documents 1 and 2, cited in the international search report, disclose treatment of pluripotent cells from bone marrow with DMSO or S-azacytidine and retinoic acid to bring about differentiation into cardiomyocytes via myocardial precursor cells, and differentiation of human stem cells into cardiomyocytes after grafting into rat myocardium. They further disclose expression of Nkx2.5, TEF-1, GATA4, MEF2D and MEF2A in regions of cardiac development in vivo. It is highly probable that the cells disclosed in Documents 1 and 2 do not take up Hoechst33342. Therefore, the inventions set forth in Claims 1-6, 19-24, 26-41, 47, 52-58, 60, 64-65, 90 and 91 are not novel over the aforementioned disclosures in Documents 1 and 2.

Moreover, murine bone marrow pluripotent stem cell line BMSC (FERM BP-7043) claimed in Claim 25 does not appear to offer any surprising effect compared with other stem cells and could be deduced easily by a person skilled in the art from aforementioned disclosures in Documents 1 and 2; therefore this does not involve an inventive step.

Use of factors expressed during the development of a given organ to prepare agents directed towards the formation of the target organ is also known art; therefore, a person skilled in the art could easily use factors disclosed in Document 1 or 2 as being expressed in regions of cardiac development to prepare myocardiogenic agents. Therefore, the inventions set forth in Claims 67-75 do not involve an inventive step.

Similarly, the amino acid sequences cited in Claims 51, 59, 66, 70 and 74 are all known; therefore, a person skilled in the art could easily use a demethylase, cytokine and transcription factor having these sequences.

Moreover, use of pluripotent cells to prepare medicaments for organ regeneration, use of genes for introducing characteristics into a host, raising of antibodies against said cells, use of the resulting antibodies in order to select cells which react with said antibodies and application for screening different substances are also common known practices. Therefore, the inventions set forth in Claims 77 and 79-85 do not involve an inventive step in the light of the inventions disclosed in Documents 1-4.

The invention set forth in Claim 86 is also not novel, because stem cells commonly express telomerase. Moreover, a person skilled in the art could easily use cells disclosed in Document 1 for medicinal applications, and the sequence cited in Claim 87 is known; therefore, the inventions set forth in Claims 87-89 do not involve an inventive step.

Documents 3 and 4, cited in the international search report, disclose the differentiation of totipotent stem cells into cardiomyocytes. Therefore, Claims 7, 19-24, 26-41, 45-47, 52-58, 90 and 91 are not novel over the aforementioned disclosures in Documents 3 and 4. Document 5 discloses the efficient differentiation of stem cells

into adipose cells after treatment with the PPARγ activator thiazolidinedione. Therefore, Claims 42-44 and 61-63 are not novel over the aforementioned disclosure in Document 5.

Documents 6-8 disclose the preparation of stem cell cell-surface factors by using CD antibodies. Therefore, given the inventions disclosed in Documents 6-8, a person skilled in the art could easily use known CD antibodies in order to isolate stem cells expressing desired cell-surface factors, and the inventions set forth in Claims 8-18 and 48-50 do not involve an inventive step.